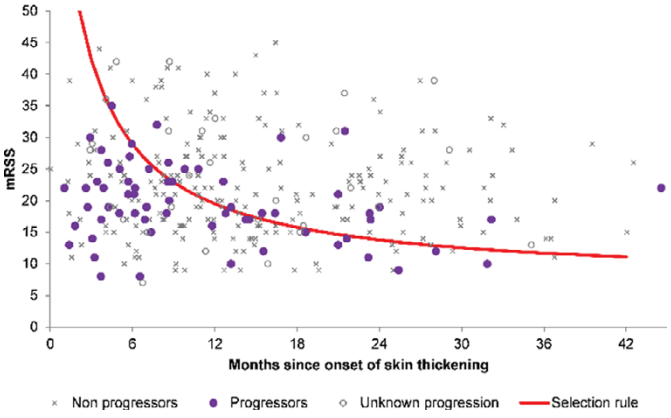
OP0123 PREDICTION OF PROGRESSIVE SKIN THICKENING IN EARLY DIFFUSE SYSTEMIC SCLEROSIS USING THREE-MONTHLY SKIN SCORES FROM THE EUROPEAN SCLERODERMA OBSERVATIONAL STUDY (ESOS)

A. Herrick[1], S. Peytrignet[1], X. Pan[1], R. Hesselstrand[2], L. Mouthon[3], E. Brown[1], L. Czirják[4], J.H. Distler[5], O. Distler[6], K. Fligelstone[1], W. Gregory[1], R. Ochiel[7], A. Silman[8], M. Vonk[9], M. Lunt[1], C. Denton[7]. *[1]University of Manchester, Manchester, United Kingdom; [2]Lund University, Lund, Sweden; [3]Université Paris Descartes, Paris, France; [4]University of Pécs, Pécs, Hungary; [5]University of Erlangen-Nuremberg, Erlangen, Germany; [6]University Hospital Zurich, Zurich, Switzerland; [7]University College London, London; [8]University of Oxford, Oxford, United Kingdom; [9]Nijmegen University, Nijmegen, Netherlands*

Background: ESOS (European Scleroderma Observational Study) was a prospective observational study of early diffuse cutaneous systemic sclerosis, recruiting from 50 centres in 19 countries and thus providing a unique opportunity to study parameters of disease progression at regular intervals.
Objectives: To describe the characteristics of patients with progressive skin thickening and derive prediction models for progression over 12 months.
Methods: Duration of skin thickening and autoantibody status (anti-topoisomerase-1[anti-Scl-70, TOPO], anti-RNA polymerase III[Pol3], anticentromere[ACA]) were documented. The modified Rodnan skin score (mRSS) was recorded 3-monthly for up to two years after baseline. The main outcome was the progression of mRSS. Progressive patients ("progressors") had to meet a 5-unit and 25% increase in their mRSS within the first 12 monthsof follow-up. Features of progressors vs. non-progressors were compared using the Fisher or Kruskal-Wallis test (for categorical and continuous variables), as were progression parameters between autoantibody groups. Logistic models were fitted to predict progression and, using ROC curves, were compared based on AUC, accuracy and positive predictive value (PPV).
Results: 326 patients were recruited, with median disease duration of 11.9 months. During the first 12 months, 66 patients (20.3%) progressed, 227 (69.6%) did not and 33 (10.1%) could not have their status assessed. At baseline, progressors had shorter disease duration than non-progressors: 8.1 months vs. 12.6 months (p=0.001). Progressors started with a lower mRSS, median 19 units vs. 21 for non-progressors (p=0.030).
124 patients were TOPO+, 50 were Pol3+, 20 were ACA+, 2 were TOPO+/ACA+ and 68 had none. Pol3+ patients had a higher mRSS peak (35 units vs. 27 overall[p=0.001]) and did so earlier (median 17.9 months vs. 23.1 months overall[p=0.214]).
Using an mRSS 22 cutoff point to predict progression in the ESOS cohort (as suggested in the literature) would yield a PPV of 24.3%, a weak improvement from the observed 20.3% share of progressors. A first model (Model A, with mRSS, duration of skin thickening and their interaction) had an accuracy of 60.9%, AUC of 0.67 and PPV of 33.8%. Figure 1summarizes the prediction rule, with patients under the curved line predicted to progress. By adding a variable for being Pol3+ (Model B), the model reached an accuracy of 71%, AUC of 0.71 and PPV of 41%.

Figure 1. Trade-off at baseline between mRSS and disease duration and prediction rule to select progressors (Model A)



Conclusions: 1. Patients with shorter disease duration and a lower mRSS have a higher likelihood of being progressors, with a trade-off between the two.
2. Pol3+ patients experience higher mRSS peaks and tend to reach them earlier.
3. Two prediction models for progressive thickening were derived. The advantage of having two is that Model B, while more accurate and useful in identifying high-risk patients in clinical practice, risks being too restrictive for patient selection into trials and may over-represent Pol3+ patients.
Disclosure of Interest: None declared
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OP0124 TREATMENT WITH CYCLOPHOSPHAMIDE FOR SYSTEMIC SCLEROSIS-RELATED INTERSTITIAL LUNG DISEASE DOES NOT IMPROVE SURVIVAL AFTER 12 YEARS OF FOLLOW UP

E.R. Volkmann[1], M. Sim[1], D.P. Tashkin[1], D. Khanna[2], P.J. Clements[1], M. Roth[1], D. Furst[1], A. Pickney[3], E. Goldmuntz[4], L. Keyes-Elstein[3], R. Elashoff[1], K. Sullivan[5] on behalf of SLS I working group. *[1]University of California, Los Angeles, Los Angeles; [2]University of Michigan, Ann Arbor; [3]Rho Federal Systems, Inc., Chapel Hill; [4]DAIT, Niaid/Nih, Bethesda; [5]Duke University, Durham, United States*

Background: Treatment with cyclophosphamide (CYC) is associated with short-term improvements in lung function, dyspnea, and radiographic fibrosis in patients with systemic sclerosis-related interstitial lung disease (SSc-ILD).[1] However, the effects of CYC therapy on long-term morbidity and mortality outcomes are unknown.
Objectives: To determine whether 1 year of treatment with CYC for SSc-ILD affects long-term morbidity and mortality in patients who participated in the Scleroderma Lung Study (SLS) I.[1]
Methods: SLS I randomized 158 SSc-ILD patients from 13 US SSc centers to 1 year of oral CYC versus placebo. The primary endpoint was the change in FVC%>predicted over 1 year. Twelve years after the study commenced, each study center contacted enrolled patients or designated surrogates to assess the following: mortality, cause of mortality, development of organ failure, need for transplant and functional status. We used counting process cox proportional hazard modeling to determine the variables associated with survival. The model findings were validated using a joint model of longitudinal and survival data. We also tested the model using long-term follow-up data from SLS II (CYC vs. Mycophenolate).
Results: Nearly half of all SLS I patients (43%) died during the follow-up period, and only 24% remained alive in the absence of organ failure. The median follow up period for all patients was 8 years. Where known, the cause of death was attributable most often to SSc. Among patients who developed malignancy (N=13), a similar proportion were treated with CYC compared with placebo. The most common type of organ failure was respiratory failure (N=31 of 33 organ failures) defined as the need for supplemental oxygen therapy (N=29) and/or lung transplantation (N=3). There was no difference in the time to death (Figure 1), or time to organ failure, or time to malignancy in patients randomized to CYC versus placebo. The Cox model identified the following variables as the most important predictors of mortality: baseline skin score (HR 1.033; P=0.0038), age at randomization (HR 1.056; $P<0.0001$), and the course of the FVC from baseline to 24 months (HR 0.975; P=0.0215). The course of the FVC was a better predictor of mortality than the baseline FVC. The joint model identified the same variables associated with mortality.

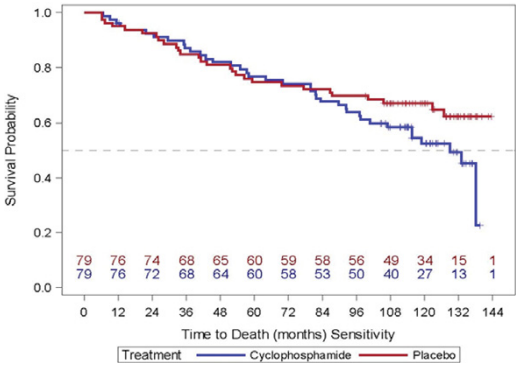

Figure 1. Time to death in patients randomized to CYC (blue line) and placebo (red line).

Conclusions: Treatment with 1-year of oral CYC for SSc-ILD does not decrease long-term mortality, organ failure or malignancy compared with placebo. In addition to identifying traditional mortality risk factors in SSc (i.e. increased skin score and advanced age), this study found that progression of the FVC over 2 years was a more important predictor of mortality than the baseline FVC. These findings suggest that early changes in surrogate measures of SSc-ILD progression may have important effects on long-term outcomes.
References:
[1] Tashkin et al. NEJM 2006;354:2655.
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OP0125 MORTALITY IN PATIENTS WITH DERMATOMYOSITIS/POLYMYOSITIS IN A CHINESE MEDICAL CENTRE

X. Yang. *Peking University First Hospital, Beijing, China*

Objectives: To investigate the mortality and the causes of death in Chinese patients with dermatomyositis (DM) or polymyositis (PM).
Methods: We collected the clinical data of all DM/PM patients in Rheumatology

department of Peking University First Hospital from January 2007 to May 2016.The primary causes of death were identified, the standardised mortality ratio (SMR) and years of life lost (YLL) were calculated based on the National Bureau of Statistics of China for the general population, the survival in the first decade was performed using Kaplan-Meier analysis, and the predictors of mortality were evaluated by multivariable cox regression.

Results: A total of 226 DM and 54 PM cases were included and the mean age of onset was 49.9±14.8 years for DM and 48.1±17.1 years for PM. The median follow-up duration was 40.6 (11.6–77.6) months. Among 267 patients who were successfully traced, 66 patients died. Infection (50.0%) was the leading cause of death followed by malignancy (19.7%), and interstitial lung disease (ILD) (9.1%). The overall age and sex adjusted SMR was 9.0 (95% CI 6.8–11.2) for DM, and 5.0 (95% CI 2.4–7.5) for PM. The overall age and sex adjusted SMR of DM/PM patients with ILD was 8.4 (95% CI 5.8–11.0), and the SMR of the patients with malignancy was 14.9 (95% CI 8.5–21.2). The YLL of women and men were 37.5 and 28.4 years respectively for DM, and 24.3 and 12.0 years respectively for PM (Table1). The 10-year survival of patients with ILD or malignancy was significantly worse than those without ILD or malignancy respectively (Figure 1 and 2). The independent predictors of mortality for DM were age of disease onset, respiratory muscle involvement and malignancy; and the independent predictor of mortality for PM was age at disease onset (Table2).

Table 1. The standardized mortality ratio (SMR), life expectancy (LE) and years of life lost (YLL)

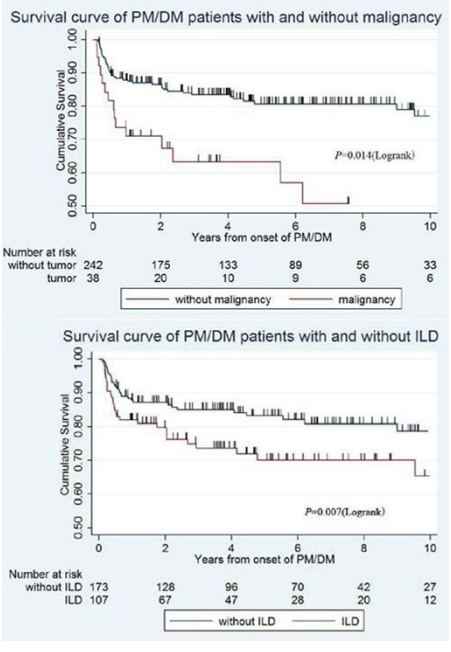
	Overall (n=280)	Females (n=201)	Males (n=79)
Dermatomyositis	226	163	63
Death number	55	37	18
SMR (95% CI)	9.0 (6.8–11.2)	12.0 (6.8–11.2)	6.0 (3.2–8.7)
LE of general population (years)	–	80.8	75.8
LE of DM patients (years)	–	43.3	47.4
YLL (years)	–	37.5 8	28.4
Polymyositis	54	38	16
Death number	11	8	3
SMR (95% CI)	5.0 (2.4–7.5)	4.2 (1.3–7.2)	9.3 (-1.2–19.8)
LE of general population (years)	–	80.8	75.8
LE of PM patients (years)	–	56.5	63.8
YLL (years)	–	24.3	12.0

Abbreviations: DM: dermatomyositis; SMR: standardised mortality ratio; CI: confidence interval; LE: life expectancy; YLL: years of life lost; PM: polymyositis.

Table 2. Multivariable cox regression analyses of risk factors in the DM/PM patients

Variables	HR	95% CI	*P* value
Dermatomyositis			
Age*	1.04	1.01–1.06	<0.001
ILD	1.35	0.74–2.48	0.319
Respiratory muscle involvement	2.58	1.19–5.58	0.016
Malignancy	3.12	1.49–6.58	0.003
Polymyositis			
Age*	1.08	1.00–1.16	0.044
ILD	2.47	0.18–34.00	0.500
ESR	1.02	0.99–1.04	0.174

*Age: Age at disease onset. Abbreviations: HR: Hazard Ratio; CI: confidence interval; ILD: interstitial lung disease; ESR: erythrocyte sedimentation rate.



Conclusions: Mortality of DM/PM patients in China is substantial, especially in females, and those with ILD or malignancy. Infection was the leading cause of death. Patients with older age at onset, respiratory muscle involvement, ILD, and malignancy need to be paid more attention.

Disclosure of Interest: None declared

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OP0126 A PHASE 2 STUDY OF SAFETY AND EFFICACY OF ANABASUM (JBT-101) IN SYSTEMIC SCLEROSIS

R. Spiera[1], L. Hummers[2], L. Chung[3], T. Frech[4], R. Domsic[5], D. Furst[6], J. Gordon[1], M. Mayes[7], R. Simms[8], S. Constantine[9], B. White[9]. *[1]Hospital for Special Surgery, New York City; [2]Johns Hopkins, Baltimore; [3]Stanford, Palo Alto; [4]University of Utah, Salt Lake City; [5]University of Pittsburgh, Pittsburgh; [6]Arthritis Association of Southern California, Los Angeles; [7]University of Texas, Houston; [8]Boston University, Boston; [9]Corbus Pharmaceuticals, Inc., Norwood, United States*

Background: Anabasum (JBT-101) is a synthetic, oral, non-immunosuppressive, preferential CB2 agonist. It inhibits onset and activates resolution of innate immune responses in animal models of systemic sclerosis (SSc).

Objectives: Evaluate safety and efficacy of anabasum in SSc

Methods: A double-blind, randomized, placebo (PBO)-controlled Phase 2 trial dosed 42 diffuse cutaneous SSc subjects with disease duration ≤6 years on stable medication including immunosuppressive drugs. Subjects received anabasum 5 mg QD, 20 mg QD, or 20 mg BID on Days 1–28, then 20 mg BID on Days 29–84, or PBO on Days 1–84. Subjects were followed off study drug on Days 85–113. The primary safety outcome was treatment-emergent adverse events (TEAEs). The primary efficacy outcome was improvement in ACR Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score, combined anabasum group vs PBO, Days 29–113 (end of Weeks 4–16). The five domains of the ACR CRISS are the modified Rodnan skin score, HAQ-DI, patient and physician global assessments, and FVC % predicted.

Results: Of 42 dosed subjects, 27 (64%) received anabasum and 15 (36%) received PBO. Three anabasum subjects withdrew: 1 (3.7%) for a TEAE of moderate dizziness; 1 withdrew consent; and 1 by physician decision. One PBO subject withdrew consent. Baseline demographic and CRISS domain scores were similar except slightly more anabasum subjects used background immunosuppressive drugs (93% versus 80%, anabasum vs PBO). Seventeen (63%) anabasum subjects had 66 TEAEs, and 9 (60%) PBO subjects had 35 TEAEs. There were no serious, severe, or unexpected TEAEs related to anabasum. Severity and relationship of TEAEs to study drug were similar in both groups. The most frequent TEAEs by MedDRA system (% anabasum vs % PBO) were: nervous system (37% vs 27%); general disorders (30% vs 7%); gastrointestinal (22% vs 20%); infections (22% vs 20%); musculoskeletal (22% vs 13%); and investigations (0% vs 20%). The most frequent TEAEs in anabasum subjects were dizziness (22%) and fatigue (19%) which were usually mild. Anabasum subjects had greater improvement in ACR CRISS scores than PBO subjects (mixed model repeated measures analysis, p=0.044, 1-sided). The median ACR CRISS scores at the end of Weeks 4, 8, 12, and 16 (anabasum vs PBO) were 3.0% vs 1.0%, 19.0% vs 1.0%, 27.5% vs 1.0%, and 33.0% vs 1.0%, respectively. Among anabasum subjects, ∼50% had ACR CRISS ≥20% after 8 weeks of dosing. The individual domains of the ACR CRISS score showed greater improvement, improvement that reached minimal important differences in several domains, and less worsening in anabasum vs PBO groups. Anabasum subjects had greater improvement in SSc skin symptoms and itch. Plasma metabolipidomic profiles showed anabasum, not PBO, shifted lipid mediator production to increase pro-resolving vs pro-inflammatory lipid mediators.

Conclusions: Anabasum provided significant and medically meaningful efficacy in SSc as assessed by the ACR CRISS score and its individual domains and had acceptable safety and tolerability in this Phase 2 trial. These data support continued clinical development of anabasum for the treatment of SSc.

Disclosure of Interest: R. Spiera: None declared, L. Hummers: None declared, L. Chung: None declared, T. Frech: None declared, R. Domsic: None declared, D. Furst: None declared, J. Gordon: None declared, M. Mayes: None declared, R. Simms: None declared, S. Constantine Employee of: Corbus Pharmaceuticals, Inc., B. White Employee of: Corbus Pharmaceuticals, Inc.

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OP0127 TEN YEARS FOLLOW-UP OF GASTROINTESTINAL INVOLVEMENT BY THE SMALL INTESTINAL CLEARANCE IN PATIENTS WITH SYSTEMIC SCLEROSIS

N. Hashimoto[1], M. Kitano[2], T. Nakazawa[3], T. Iwasaki[4], T. Hashimoto[1]. *[1]Hashimoto Rheumatology Clinic, Osaka; [2]Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya; [3]Osaka Saiseikai Nakatsu Hospital, Osaka; [4]Department of Pharmacy, Hyogo University of Health Sciences, Kobe, Japan*

Background: Systemic sclerosis (SSc) is an inflammatory autoimmune disease characterized by fibrosis and small vascular involvement in the skin, lungs, heart and gastrointestinal (GI) tract. The esophagus is the most frequently involved GI tract disorder. Although the small intestinal involvement such as malabsorption and pseudo-obstruction is less common, it has been related to morbidity and mortality of SSc patients. We previously reported a close correlation between the